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AUTHOR: Kaye J A
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CORPORATE SOURCE: Division of Oral Medicine Oral and Maxillofacial Surgery, and Dentistry, Brigham & Women's Hospital, Boston, MA 02115, USA.
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Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review

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Abstract

Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. The agents and methods that have been used and studied in chemotherapy- and radiotherapy-induced oral mucositis, their mechanisms of action, and the current knowledge of their efficiency to reduce the incidence, severity or shorten the duration of oral mucositis are reviewed in this article. Oral cooling is a cheap and available method to lower the severity of bolus 5-fluorouracil-induced oral mucositis. However, more effective methods are needed. Results of studies with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor are promising. Lasers are partly beneficial, but equipment-demanding. Modification of the chemotherapy regimen resulting in shortening of the exposition time to chemotherapy agents or chronomodulation of chemotherapy has been shown to lower mucosal toxicity of some regimens. Results of animal studies with locally applied transforming growth factor β3 and interleukin-11 are also promising. Based on the findings of the role of the inflammatory cascade in the response of normal tissues to chemotherapy and radiotherapy, anti-inflammatory drugs might be beneficial. At the present time, no agent has been shown to be uniformly efficacious and can be accepted as standard therapy of chemotherapy- and radiotherapy-induced oral mucositis. Further intensive research is needed.

Keywords: Stomatitis prevention; Stomatitis control; Antineoplastic agents; Chemically induced; Radiotherapy-adverse effects

1. Introduction

Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. Due to severe painfulness, oral mucositis interferes with the patient's quality of life and nutrition. It also increases the risk of systemic infections in immunocompromised patients due to disrupted barriers and often is the dose-limiting factor interfering with the intensification of anticancer therapy [1–3].

Oral mucositis is a consequence of the toxic effects of chemotherapeutic agents and irradiation on oral mucosa cells [2,4,5]. A complex hypothesis has been proposed as to the mechanism by which mucositis develops and resolves; it is based on four phases: an initial inflammatory/vascular phase; an epithelial phase; an ulcerative/bacteriological phase; and a healing phase [5]. The inflammatory response induced in the involved tissues by chemotherapy and ionizing radiation occurs through the activation of intracellular and intercellular signaling pathways regulating gene expression of specific proteins involved in immune and inflammatory processes, such as cytokines, adhesion molecules, etc. [6–9]. The specific intracellular damage induced by cytotoxic drugs and responsible for the epithelial phase of mucositis development is generally well characterized [5]. In addition, recent studies have shown that most anticancer agents and γ irradiation kill cells by a common death program called apoptosis, which is the usual form of physiologic cell death in eukaryotic cells directed by a machinery that consists of molecular pathways discovered during the past several years [10–12]. Apoptosis may be involved in the development of chemotherapy- and radiotherapy-induced oral mucositis.

The role of oral bacterial colonization in the development of chemotherapy- and radiotherapy-induced oral mucositis is controversial. The appearance and resolution of oral mucositis is often considered to be linked to

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chemotherapy-induced neutropenia [13–15], which predisposes patients to oral infections, that could aggravate severity or prolong duration of oral mucositis [16]. The role of infection in the etiology of toxic oral mucositis is supported by the findings of abnormal oral flora colonization [17–22]. The role of gram-negative bacteria or endotoxin (lipopolysaccharide) may be in potentiation of the immune response of the tissues to chemotherapeutic agents or irradiation, since endotoxin is a potent inflammation mediator [8,20]. On the other hand, however, oral mucositis complicates chemotherapy regimens that are relatively nonmyelotoxic; its grade or recovery does not correlate with the presence, severity or recovery of neutropenia in some reports [16,23–27]; and locally applied antimicrobials, desinficientia and antimycotics failed to substantially influence our ability to prevent or heal it [28–33].

The clinical appearance of oral mucositis may range from mild discomfort and erythema to painful erythema, and oedema and/or ulcerations [2,21].

The agents and methods that have been used and studied in chemotherapy- and radiotherapy-induced oral mucositis, their mechanisms of action, and the current knowledge of their ability to reduce the incidence, severity or shorten the duration of oral mucositis are reviewed in this article (Table 1). As many drugs have been studied and tried with either intention, prevention and treatment are dealt with together. Symptomatic therapy of this complication is beyond the scope of this paper and is reviewed elsewhere [2,3,34].

2. Locally applied measures and pharmacotherapeutics

Dental restoration to healthy status, including therapy of dental caries, periodontal disease, detection of foci, and correction of any other potential sources of irritation, such as ill-fitting prostheses and orthodontic appliances, is advised before or early in cancer therapy in order to reduce the frequency of oral problems [35–39]. Although a retrospective study has shown a substantial decrease in the frequency of oral mucositis in the period of aggressive dental interventions compared to the previous one, when no such measures were used [36], results of a prospective study focused on the superiority of an intensive dental care and oral hygiene protocol were not clinically impressive [40].

Oral hygiene programs are commonly advised to reduce the amount and activity of oral microflora and to prevent or reduce discomfort associated with oral mucositis [2,20,35,41–44]. Patients are instructed about an effective and frequent mechanical plaque removal by daily brushing with a soft toothbrush, flossing with dental floss and rinsing with saline solution and mild solution of sodium bicarbonate, about lip lubrication, 'sugarfree' products to enhance oral moistness or saliva substitutes, when needed [2,35,37,38,41]. An early beginning of proper oral care reduced oral toxicity of radiotherapy in a pilot study [45]. Although statistically significant, the superiority of an intensive oral hygiene protocol involving initial treatment of dental lesions and tooth and gum brushing during aplasia was not clinically useful compared to a limited oral hygiene protocol in bone marrow transplantation (BMT) patients [40].

Sucralfate is a basic aluminum salt of sucrose octasulfate useful in the treatment of peptic ulcer disease [46]. The mechanism of action of this drug is not known with certainty, but it may involve the binding of sucralfate to the damaged mucosal surface proteins and the formation of a protective coating over ulcers with possible epithelial regeneration and angiogenesis-promoting properties [47–50]. Anecdotal reports suggested pronounced responses to oral sucralfate in patients with chemotherapy-induced oral mucositis [51–53], supported by results of several studies [54–58]. However, there was seen no statistically significant reduction in mucositis in other, randomized double-blind studies [59–63]. Sucralfate can reduce the experience of pain [55,59,60,62,63]. Another mouth-coating agent, *kaolin pectin*, combined with diphenhydramine, which is a H1-histamine antagonist and local anesthetic, was able to reduce oral pain without reducing the degree of mucositis [64].

Vitamin E probably acts as an antioxidant; it presumably inhibits oxidation of essential cellular constituents and prevents the formation of toxic oxidation products [65–67]. Reactive oxygen intermediates are important in the activation of inflammatory tissue response [9]. Although the antioxidant effects of vitamin E are relatively weak [68], duration of chemotherapy-induced oral mucositis was significantly shorter in patients treated topically with vitamin E than in the placebo group in two small studies [69,70].

Tretinoin (all-trans-retinoic acid), a vitamin A derivative, is known to stimulate wound healing [71]; it has anti-inflammatory effects that may create better local circumstances for healing [72]; besides that, it induces epithelial growth via cell differentiation modulation [73]. It has been reported to significantly reduce the severity of oral mucositis in BMT patients [74].

Hydrogen peroxide, once recommended as an oral rinse to aid in the management of adhesive mucus and for its antimicrobial properties [75,76], came into disrepute because of its antifibroblast healing-delaying and possible carcinogenic activity [18,41]. In addition, frequent mechanical cleansing of the mouth has been reported more beneficial than hydrogen peroxide [44].

Chlorhexidine is a powerful broadly active antimicrobial and antiseptic. Assuming that oral mucositis in patients undegoing intensive antineoplastic treatments results largely from superinfection of a reversibly

Table 1
Drugs and methods studied in the prevention and/or therapy of chemotherapy- or radiotherapy-induced oral mucositis (survey of published studies)[a]

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
I. Locally applied measures and pharmacotherapeutics						
a. Dental restoration						
[36]	495	CHT	No/no/no	P	Dental intervention in standardized protocols; compared to a published study without these measures	Substantial reduction in frequency
[40]	150 (75/75)	CHT (ev. BMT)	Yes/yes/no	P	Intensive versus limited protocol (i.e. with vs without initial treatment of dental lesions, tooth and gum brushing)	Significant reduction, not clinically impressive
b. Oral hygiene						
[45]	30 (10/10/10)	RT	Yes/yes/no	P	Instructions on oral care given at 1 day versus 1 week before RT versus no instructions	Significant reduction in the 2nd group
[40]	150 (75/75)	CHT (ev. BMT)	Yes/yes/no	P	Intensive versus limited protocol (i.e. with vs without initial treatment of dental lesions, tooth and gum brushing)	Significant reduction, not clinically impressive
c. Mouth-coating agents:						
·Sucralfate						
[51]	4	CHT	No/no	T		Accelerated healing
[52]	23	CHT	No/no	T, P		Reduction
[53]	18	CHT	No/no	T		Reduction mostly
[54]	46 (23/23)	5-FU-CHT	Yes/yes/yes	P	Sucralfate versus placebo	Significant reduction
[55]	45 (24/21)	RT	Yes/yes/no	P	Sucralfate yes versus no	Significant reduction
[56]	40 (20 + 20)	RT	No/no	P, T	P: sucralfate, later + fluconazole, T: sucralfate + fluconazole	Reduction
[57]	48 (24/24)	RT	Yes/yes/yes	P	Sucralfate versus placebo	Significant temporary reduction
[58]	45	5-FU	No/no	P		Low incidence
[59]	48 (24/24)	CHT	Yes/yes/yes	P + T	Sucralfate versus placebo	No difference (less pain)
[60]	33 (16/17)	RT	Yes/yes/yes	P + T	Sucralfate versus placebo	No difference (less pain)
[61]	40 (20/20)	RT	Yes/yes/yes	P	Sucralfate versus placebo	No difference
[62]	50 (27/23)	5-FU	Yes/yes/yes	T	Sucralfate versus placebo	No difference (less pain)
[63]	111(53/58)	RT	Yes/yes/yes	T	Antacid + diphenhydramine + viscous lidocaine with versus without sucralfate	No difference (less pain)
·Kaolin-pectin						
[64]	29 (7/7/15)	RT	Yes/yes/yes	P + T	Oral hygiene + sucralfate versus + diphenhydramine + kaolin-pectin versus historical group without oral hygiene or rinse	No difference between study groups (less pain than in historical group)
d. Vitamins:						
·Vitamin E						
[69]	18 (9/9)	CHT	Yes/yes/yes	T	Vitamin E versus placebo	Significant reduction of duration
[70]	19 (10/9)	CHT (ev. BMT)	Yes/yes/no	P	Vitamin E versus placebo	Significant reduction in leukemia patients, no difference in other groups

(Table continued on next page)

Table 1 (*continued*)

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
•Tretinoin						
[74]	11 (6/5)	CHT, CHRT (BMT)	Yes/yes/no	P	Tretinoin yes or no	Significant reduction of severity
e. Antibiotics, desinficientia:						
•Hydrogen peroxide						
[44]	40 (20/20)	RT	Yes/yes/no	P	Hydrogen peroxide versus saline solution	Significantly worse outcome
•Chlorhexidin						
[77]	16 (8/8)	CHT	Yes/yes/yes	P	Chlorhexidine versus placebo	Significant reduction
[78]	51 (24/27)	CHRT (BMT)	Yes/yes/yes	P	Chlorhexidine versus placebo	Significant reduction
[79]	40 (19/21)	CHT	Yes/yes/yes	P+T	Chlorhexidine versus placebo	Significant reduction
[79]	30 (16/14)	RT	Yes/yes/yes	P+T	Chlorhexidine versus placebo	No difference
[80]	13 (6/7)	CHT (ev. BMT)	Yes/yes/yes	P	Chlorhexidine versus placebo	Significant reduction in BMT patients, no difference in non-BMT patients
[28]	100 (50/50)	CHRT (BMT)	Yes/yes/yes	P	Chlorhexidine versus placebo	No difference
[29]	30 (15/15)	RT	Yes/yes/yes	P+T	Chlorhexidine versus placebo	No difference
[30]	86 (34/16/18/18)	CHT, BMT	Yes/yes/no	P	Chlorhexidine + nystatin versus nystatin versus chlorhexidine versus saline solution	No difference
[31]	52 (25/27)	RT	Yes/yes/yes	P	Chlorhexidine versus placebo	Slight aggravation (more discomfort)
[81]	28 (14/14)	CHT	Yes/yes/no	P	Chlorhexidine yes versus no	No difference
[82]	222 (111/111)	CHT	Yes/yes/yes	P	Chlorhexidine versus placebo	No difference
•Povidone-iodine solution						
[83]	40 (20/20)	CHRT	Yes/yes/no	P	Povidone-iodine versus placebo	Significant reduction
•Selective decontamination						
[20]	15	RT	No/yes/no	P	Lozenges of polymyxine E, tobramycin, ampho B compared to historical controls (chlorhexidine, placebo) [39]	Significant reduction
[89]	59 (22/37)	RT	Yes/yes/no	P	Sucralfate + (ciprofloxacin or ampicilin) + clotrimazole versus sucralfate	Reduction
[22]	221 (112/109)	RT	Yes/yes/yes	P	Lozenges of polymyxin, tobramycin, ampho B versus placebo	No difference in severe grades incidence; significant distribution reduction
[32]	26 (12/14)	CHT, CHRT (BMT)	Yes/yes/no	T	Polymyxin E, tobramycin and ampho B with chlorhexidin versus diphenhydramine, magnesia-alumina, lidocaine	Significant reduction, not clinically impressive
[33]	112 (54/58)	RT	Yes/yes/yes	P+T	Lozenges of polymyxine E, tobramycin, ampho B versus placebo	No objective difference, significant reduction in patient-reported mucositis
f. Anti-inflammatory agents:						
•Chamomila						
[41]	20	RT	No/yes/no	P	Compared with a historical group without chamomila	Reduction compared to previous
	32	CHT	No/yes/no	T	Compared with a historical group without chamomila	Short duration
	46	CHT	No/yes/no	P	Compared with a historical group without chamomila	Low incidence
[91]	164 (82/82)	5-FU	Yes/yes/yes	P	Chamomila versus placebo	No difference
•Betamethasone						
[94]	5	RT	No/no	P	High-dose betamethasone	Total prevention of mucositis

Table 1 (*continued*)

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
·Benzydamin						
[98]	67 (37/30)	RT	Yes/yes/yes	P, T	Benzydamine versus placebo	Significant reduction (less pain)
[99]	36 (19/17)	CHT, RT	Yes/yes/yes	P, T	Benzydamine versus placebo	Significant reduction
[100]	43 (25/18)	RT	Yes/yes/yes	P, T	Benzydamine versus placebo	Significant reduction
[101]	25 (13/12)	RT	Yes/no/no	P	Benzydamine versus chlorhexidine	No difference (more discomfort)
·Mesalazine						
[109]	14 (14 cc/14cc)	CHT (ev. BMT)	No/yes/no	T	Mesalazine yes versus no	(Less pain)
g. Cytokines:						
·GM-CSF						
[27]	24	CHT	No/no	T		Reduction
[110]	45 (9/9/9/9/9)	CHT	Yes/yes/yes	P	GM-CSF at four various concentrations versus placebo	No significant reduction, aggravation in low-dose drug groups; no dose response
·TGF-β3						
No studies in humans available						
·EGF						
[116]	12 (6/6)	CHT	Yes/yes/yes	T	EGF versus placebo	No difference
h. Eicosanoids:						
·PGE_1 (misoprostol)						
[118]	15 (8/7)	CHT (PSCT)	Yes/yes/yes	P	PGE_1 versus placebo	Significant aggravation
·PGE_2						
[120]	8	CHT	No/no	P, T		Successful prophylaxis and reduction
[121]	24 (10/14)	CHRT	No/yes/no	P	PGE_2 Yes or no	Significant reduction (less pain)
[122]	15	CHRT	No/no	T		No severe grades
[123]	60 (31/29)	CHT, CHRT (BMT)	Yes/yes/yes	P	PGE_2 or placebo	No difference
i. Multiagent topical mouthrinses						
[18]	79	CHRT	No/no	P, T	Hydrogen peroxide + polyvinylpyrrolidon-iod + nystatin + 5% dexpanthenol solution	Reduction, accelerated healing
[126]	12 (7/5)	RT	Yes/yes/yes	P	Hydrocortison + nystatin + tetracycline + diphenhydramine versus placebo	Significant reduction
j. Epitelization promoting agents:						
·Silver nitrate						
[128]	16 (16ss/16ss)	RT	No/yes/no	P	Applied to one side of buccal mucosa, the contralateral one served as control	Significant reduction
[130]	10 (10ss/10ss)	RT	No/yes/no	P	Applied to one side of buccal mucosa, the contralateral one served as control	No difference
k. Antineoplastic agent antagonists:						
·Leucovorin						
[132]	14 (14cc/14cc)	HD-MTX	No/yes/no	P	Leucovorin + hyaluronidase yes versus no	No difference
[133]	13 (44cc)	HD-MTX	No/no	P		No benefit

(Table continued on next page)

Table 1 (*continued*)

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
l. Allopurinol						
[139]	6 (6cc/6cc)	5-FU	No/yes/no	P	Allopurinol yes versus no	Substantial reduction
[140]	16	5-FU	No/no	P		Substantial reduction
[141]	44 (22/22)	5-FU	Yes/yes/yes	T	Allopurinol versus placebo	Significant reduction
[142]	77 (38/39)	5-FU	Yes/yes/yes	P	Allopurinol versus placebo	No difference
2. Locally applied nonpharmacological methods						
a. Radiation shields						
[144]	125 (61/64)	RT	Yes/yes/no	P	Midline mucosa-sparing blocks yes versus no	Significant reduction
b. Oral cooling (cryotherapy)						
[145]	95 (50/45)	5-FU	Yes/yes/no	P	Cryotherapy yes versus no	Significant reduction
[146]	84 (44/40)	5-FU	Yes/yes/no	P	Cryotherapy yes versus no	Significant reduction
[147]	20 (9/11)	5-FU-CHT	Yes/yes/no	P	Ice bar with fibrinolysin and deoxyribonuclease yes versus no	Significant reduction
[148]	178 (89/89)	5-FU	Yes/yes/no	P	Cryotherapy duration of 60 versus 30 min	No difference
[149]	22	L-PAM, CHT (BMT, PSCT)	No/no	P		Reduction in single-agent L-PAM, not in multiagent regimens
[150]	18	L-PAM	No/no	P		Reduction in both single agent and multiagent regimens
c. Soft lasers						
[153]	67 (25/21/21)	5-FU-CHT	No/yes/no	P, T	Laser prophylaxis/therapy yes versus no	Substantial reduction (prophylaxis), reduced duration (therapy)
[154]	59 (23/16/20)	5-FU-CHT	No/yes/no	P, T	Laser prophylaxis or therapy yes versus no	Reduction (prophylaxis group), accelerated healing (therapy group)
[155]	22 (22ss/22ss)	CHT, CHRT (BMT)	Yes/yes/yes	P	Laser on one buccal side versus sham treatment to the contralateral side	Significant reduction
[156]	30 (15/15)	CHRT (PSCT, BMT)	Yes/yes/yes	P	Laser versus sham treatment	Significant reduction
3. Systemically applied pharmacotherapeutics						
a. Antioxidants:						
•Beta carotene						
[157]	20 (10/10)	CHRT	Yes/yes/no	P	Beta-carotene enriched versus standard diet	Significant reduction
•Azelastine						
[160]	63 (37/26)	5-FU-CHRT	Yes/yes/no	P	Vitamins C + E + glutathione with versus without azelastine	Significant reduction, not clinically impressive
b. Immunomodulatory drugs:						
•Pentoxifylline						
[165]	50 (30/20)	CHT (BMT)	No/yes/no	P	Oral PTX versus historical controls without PTX	Significant reduction
[166]	92 (31/61)	CHT, CHRT (BMT)	No/yes/no	P	iv PTX versus historical controls without PTX	Significant aggravation
[167]	88 (44/44)	CHT, CHRT (BMT)	Yes/yes/no	P	Oral PTX versus placebo	No difference
[168]	140 (70/70)	CHT, CHRT (BMT)	Yes/yes/yes	P	Oral PTX versus placebo	No difference
[169]	49 (28/21)	CHT, CHRT (BMT)	No/yes/no	P	Oral PTX versus historical controls without PTX	No difference

Table 1 (*continued*)

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
[170]	10 (10cc/10cc)	5-FU-CHT	Yes/yes/yes	P	Oral PTX versus placebo	No difference
·Indomethacin						
[171]	19 (10/9)	RT	Yes/yes/yes	P	Indomethacin versus placebo	Significant delay of onset
·Immunoglobulin						
[172]	124 (79/45)	RT, CHRT	No/yes/no	T	IMIG yes versus no	Reduction
[173]	86	RT	No/no	T	IMIG	Shortened duration
[174]	81 (39/42)	RT	Yes/yes/yes	T	IMIG versus placebo	Significant reduction
[175]	42 (22/20)	RT, CHRT	No/yes/no	P	IMIG yes versus no	Significant reduction in CHRT patients, no difference in RT patients
[176]	3 (3cc/9 cc)	HD-MTX	No/yes/no	P	IVIG yes versus no	No mucositis in IVIG cc
c. Anticholinergic drugs:						
·Propantheline						
[180]	12 (6/6)	Eto-CHT (BMT)	Yes/yes/no	P	Propantheline versus placebo	Significant reduction
[181]	31	Eto-CHT (PSCT)	No/no	P	Control—published reference without propantheline	Reduction
·Atropine						
[132]	6 (6cc/6cc)	HD-MTX	No/yes/no	P	Atropine yes versus no	No benefit
d. Cytokines:						
·G-CSF, GM-CSF						
[23]	22 (18/6)	CHT	No/yes/no	P	G-CSF yes versus no	Significant reduction
[182]	33 (15/18)	CHT (BMT)	No/yes/no	P	G-CSF yes versus no	Significant reduction of duration
[183]	22 (22cc/22cc)	CHT (ev. BMT)	No/yes/no	P	GM-CSF yes versus no	Reduction
[184]	37 (23/14)	CHT	Yes/yes/no	P	GM-CSF versus placebo	Significant reduction
[185]	37	5-FU	No/no	P	GM-CSF	Reduction
[186]	26 (10/16)	CHT (BMT)	No/yes/no	P	G-CSF yes versus no	No difference
[187]	80 (41/39)	CHT	Yes/yes/no	P	G-CSF yes versus no	No difference
[188]	50 (20/30)	CHT, CHRT (BMT)	No/yes/no	P	G-CSF yes versus no	No difference
[16]	20 (9/11)	5-FU-CHT	Yes/yes/no	P	GM-CSF yes versus no	Significant reduction
[25]	26 (14/12)	CHT, CHRT (BMT)	No/yes/no	P	G-CSF yes versus no	Significant duration reduction (TBI-patients)
[189]	109 (53/56)	CHRT (BMT)	Yes/yes/yes	P	GM-CSF versus placebo	Significant reduction
[190]	14 (7/7)	CHT	Yes/yes/no	P	G-CSF yes versus no	Significant reduction
[191]	10	RT	No/no	P	GM-CSF	Low incidence
[192]	29	CHT, RT	No/no	P	GM-CSF	Reduction
·Interleukin-11						
No studies in humans available						
e. Antiviral drugs:						
·Acyclovir						
[201]	60 (28/23/9)	CHT, CHRT (BMT)	No/no	P	Acyclovir in HSV seropositive, seronegative and unknown serology patients	No difference
[203]	15 (12/3)	BMT	No/no	P	Acyclovir in seropositive patients	Majority of patients developed mucositis
[204]	34 (16/18)	CHT, RT	Yes/yes/yes	P	Acyclovir versus placebo	No difference
[205]	90 (45/45)	CHT	Yes/yes/yes	P	Acyclovir versus placebo	No difference
f. Metabolic substrate supplementation:						
·Glutamine						
[212]	14 (14cc/14cc)	CHT	No/yes/no	P	Oral glutamine yes versus no	Significant reduction
[213]	13 (13cc/13cc)	CHT	Yes/yes/yes	P	Oral glutamine versus placebo	Significant reduction
[214]	20cc (10/10)	CHT	Yes/yes/yes	P	Total parenteral nutrition with versus without glutamine	No difference
[215]	28 (14/14)	5-FU	Yes/yes/yes	P	Oral glutamine versus placebo	No difference

Table 1 (*continued*)

Reference No.	No. of patients (study/control group)	Cause	Randomized/ controlled/ double-blind?	P/T	Study characteristics	Result—impact on oral mucositis
g. Hormone:						
•Melatonin						
[216]	80 (40/40)	CHT	Yes/yes/no	P	Melatonin yes versus no	No difference
4. Other methods:						
a. Modification of the chemotherapy regimen						
[217]	43 (21/22)	HD-MTX	Yes/yes/no	P	4-h infusion of 12 g/m^2 versus 36-h infusion of 1 g/m^2	Significant reduction in the 1st group
[26]	42	5-FU-CHT	No/no	P	24-h infusion weekly, compared to published studies with 120- or 96-h infusion forth or third weekly, respectively	Substantial reduction
b. Chronotherapy						
[221]	186 (93/93)	5-FU-CHT	Yes/yes/no	P	Chronotherapy versus constant rate infusion	Significant reduction

[a] P, prophylactic use; T, therapeutic use; CHT, chemotherapeutic agents other than 5-fluorouracil, methotrexate, melphalan, etoposide; ev. BMT, BMT performed in some patients; RT, radiotherapy; 5-FU, 5-fluorouracil; 5-FU-CHT, 5-fluorouracil-based chemotherapy; CHRT, chemo-radiotherapy; BMT, bone marrow transplantation; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF-β, transforming growth factor β; EGF, epidermal growth factor; $PGE_{1,2}$, prostaglandin E_1, E_2; CHT (BMT, PSCT) or CHRT (BMT, PSCT), bone marrow or peripheral stem cell transplantation conditioning regimen; ampho B, amphotericine B; ss, buccal sides; cc, cycles; HD-MTX, high-dose methotrexate; L-PAM, melphalan; PTX, pentoxifylline; iv, intravenous; IMIG, intramuscular immunoglobulin; IVIG, intravenous immunoglobulin; Eto, etoposide; Eto-CHT, etoposide-based chemotherapy; TBI, total body irradiation; HSV, herpes simplex virus.

damaged mucosal barrier, the efficiency of chlorhexidine to reduce this complication has been intensively studied. It has been shown to be effective in several studies [77–80]; in other studies, however, there was no clinically demonstrable benefit of chlorhexidine in the prevention and treatment of irradiation- or chemotherapy-induced or BMT-related oral mucositis [28–31,79,81,82], although improved oral hygiene and some changes in oral mucosa colonization have been observed in chlorhexidine users [28–30,78]. Mouthwash-induced discomfort has been reported in the chlorhexidine arm in some studies [31,81].

Povidone-iodine solution, a disinfection agent, significantly decreased radiochemotherapy-induced oral mucositis in a study [83].

The results of various studies suggest that yeast colonization is not involved in the pathogenesis of mucositis [84–86] and identical observations were reported for viridans streptococci [29,85]. As a high oral carriage of gram-negative bacilli was found in several studies [22,29,87,88], a hypothesis was established based on the role of pathological gram-negative oral flora, maybe particularly of endotoxin, in the etiology of radiotherapy- and chemotherapy-induced oral mucositis and the concept of *selective decontamination* has been developed [20,21]. In a pilot study, lozenges containing polymyxin E, tobramycine, and amphotericine B have been used in irradiated head and neck cancer patients; successful elimination of oral gram-negative bacilli has been achieved and severe forms of irradiation oral mucositis have been prevented when compared retrospectively with patients using placebo or chlorhexidine [20]. Addition of ciprofloxacin or ampicilin and clotrimazole to the sucralfate mouthwash also reduced radiation mucositis [89]. In other studies, selective decontamination did not reach clinically significant reduction in mucositis [22,32,33].

Chamomila, a solution prepared from the flower of the chamomile plant, contains mainly chamazulene, levomenol, polyins, and flavonoids. The combination of these constituents has anti-inflammatory and spasmolytic effects and promotes granulation and epitelization [90]. Carl and Emrich [41] have observed that Kamillosan Liquidum mouthwashes applied prophylactically delayed onset and reduced severity of radiation mucositis, and prevented the occurence of severe mucositis in the majority of the patients who received systemic chemotherapy when compared with historical controls. The results of a phase III trial did not show any benefit of chamomila in 5-fluorouracil-induced oral toxicity, however [91].

Glucocorticosteroids are anti-inflammatory drugs inhibiting synthesis of inflammatory proteins with the involvement of complex mechanisms at the molecular level, which leads to the decrease in transcription of genes involved in inflammation [9,92,93]. The mucosa of five patients, who used a high-dose betamethasone mouthwash before and during radiotherapy

for malignant parotid tumors, showed progressive whitening as radiation progressed, which was in contrast to the erythema that usually occurs. The mucosa remained virtually ulcer-free and no discomfort or bleeding of oral mucosa appeared. Histological examination of the oral mucosa taken at completion of irradiation showed absence of the inflammatory component of irradiation-induced mucositis and some thickening and keratinization of the buccal epithelium [94].

Benzydamine is a non-steroidal drug that possesses topical analgesic, anaesthetic, anti-inflammatory, and antimicrobial properties [95–97]. Reduction in mucositis has been reached using benzydamine [98–100]; on the other hand, there was no reduction in another study [101]. Significant relief of pain has been observed in benzydamine users [98,102,103]. However, oral burning associated with benzydamine rinses has been noted frequently [101,103,104].

Mesalazine (5-aminosalicylic acid) is an anti-inflammatory agent [105]; salicylates have been shown to inhibit the activation of one of the transcription factors involved in the transcription of inflammatory genes, albeit only in relatively high concentrations [106]. Topical mesalazine is used in the therapy of inflammatory bowel disease [105] and has been shown to be effective in the treatment of oral aphtous ulcers [107] and of oral and genital ulceration in Behcet's disease [108]. Results of a preliminary study of topical mesalazine in the treatment of chemotherapy- and radiotherapy-induced oral mucositis showed some benefit associated with the application of this agent [109].

Studies with locally applied granulocyte-macrophage colony-stimulating factor (GM-CSF) gave conflicting results so far [27,110]. GM-CSF may have a direct stimulatory effect on the growth or regeneration of oral mucosa cells [16].

The beta transforming growth factors (TGFs-β) transiently inhibit the cycling of epithelial cells in G1 phase [111]. The TGF-β3 administration reduces proliferation of oral epithelium in vitro and in vivo and may thus decrease the susceptibility of these cells to the cytotoxic effect of chemotherapy. Topical application of TGF-β3 to oral mucosa in a hamster model prior to chemotherapy significantly reduced the incidence, severity and duration of oral mucositis [112,113].

Epidermal growth factor (EGF) has a variety of effects on epithelial proliferation, differentiation, and chemotaxis [114]. Its level has been shown to decrease in oral secretions during radiation therapy and correlate inversely with the degree of oral mucositis [115]. EGF mouthwash was not observed to accelerate healing of chemotherapy-induced oral mucositis in a small group of patients, however [116]. Moreover, hamsters receiving EGF had significantly more severe and prolonged mucositis. Despite a hypothesis that EGF exposure later may hasten re-epithelization, delayed exposure to EGF only appeared to delay the onset of mucositis and had no beneficial effects on either the severity or duration of mucositis [34].

Misoprostol is a synthetic prostaglandin E_1 analog with greater mucosal-protective activity than natural prostaglandins. It is used to prevent and treat gastrointestinal lesions induced by nonsteroidal anti-inflammatory drugs and upper gastrointestinal ulcerations [117]. In another study, misoprostol exhibited adverse effects [118].

Prostaglandin E_2 (PGE_2) is believed to possess cytoprotective properties [119]. Preliminary results suggested that topical application of PGE_2 (dinoproston) could be effective in the prevention of anticancer therapy-related oral mucositis [120–122]. In a double-blind prospective clinical trial, however, there was no significant difference in mucositis between the BMT patients dissolving PGE_2 in the mouth and those treated with placebo. In patients receiving PGE_2, a significantly higher incidence of herpes simplex virus reactivation has been documented. In the patients with herpes simplex virus infection receiving PGE_2, the incidence of severe mucosal lesions was significantly higher than in patients without herpes simplex virus infection who had received PGE_2 or in the control group [123]. Although PGE_2 is considered to possess anti-inflammatory properties [124], there are reports suggesting that endogenous PGE_2 has an important regulatory role in oral inflammation [125]. Exogenous PGE_2 may also have pro-inflammatory effects, responsible for the observed adverse effects associated with herpes simplex virus infection.

Various multiagent topical mouthrinses are used in the management of radiotherapy- or chemotherapy-induced oral mucositis. These include antimicrobial and antifungal agents combined with epithelization-promoting or mouth-coating agents, or anti-inflammatory drugs, or local anaesthetics; for instance, a combination of hydrogen peroxide plus betaisodone plus nystatine plus dexpanthenol [18], or hydrocortison plus nystatine plus tetracycline plus diphenhydramine [126], or magnesium aluminum hydroxide plus diphenhydramine plus viscous lidocaine, or nystatin plus lidocaine plus solucortef plus sucralfate plus syrup alta [34]. However, the efficacy of these regimens is difficult to assess and long-term studies supporting such treatment are not available [127].

Maciejewski et al. [128,129] have reported that oral mucosa burning with 2% *solution of silver nitrate* a few days before radiotherapy reduced the severity of mucositis. They suggested that silver nitrate can stimulate the unirradiated mucosa into a more effective proliferative state before the start of radiotherapy. In another study, local conditioning of human oral mucosa by 3% silver nitrate solution significantly increased epithelial proliferation rate in healthy volunteers. Despite this fact, the results concerning oral mucositis were not reproduced [130].

Leucovorin (5-formyltetrahydrofolate) is used to protect normal tissues from the toxic effect of high-dose methotrexate, a folic acid antagonist [131]. Leucovorin mouthwash was expected to protect oral mucosa cells by antagonizing locally the inhibition of purin- and thymidilatsynthesis induced by methotrexate. However, in several studies, topical application of leucovorin did not effectively prevent development of oral mucositis [132,133]. The saliva concentrations of methotrexate and 7-hydroxymethotrexate have been shown not to correlate with the development of oral mucositis [134].

Allopurinol is a structural isomer of hypoxanthine. Certain findings suggested that oxypurinol, the major metabolite of allopurinol, could attenuate 5-fluorouracil (5-FU)-induced toxicity by inhibiting specific enzymes involved in the formation of toxic 5-FU metabolites [135–138]. Based on these findings, an assumption was made that allopurinol mouthwash might attenuate the toxicity of 5-FU on oral mucosa. Clark and Slevin [139] have observed a decrease in 5-FU-induced oral mucositis in six patients when allopurinol mouthwash was used and some studies [140,141] supported their findings. However, a randomized, placebo-controlled, double-blind study was closed preliminary, because a planned interim analysis showed convincingly negative results [142].

3. Locally applied nonpharmacological methods

Shields can be constructed to protect uninvolved oral tissues during radiation [3,143,144]. They have been shown to significantly reduce acute toxicity of radiotherapy in the oral region [144].

Oral cooling (cryotherapy) probably causes local vasoconstriction and, thus, temporarily reduces oral mucosal blood flow and the amount of the drug delivered to oral mucosa cells. Patients swish ice chips in their mouths or mouthwash with ice-cold water for a total of 30 min, starting 5 min prior to each dose of the drug. Cryotherapy has been shown to significantly reduce bolus 5-FU-induced oral mucositis [145–147]. A 60-min duration of cryotherapy does not provide more benefit than a 30 min one [148]. 5-FU is a drug with short plasma half-life; this method cannot be used for patients treated by continuous 5-FU infusion, however [16]. Protective effect of cryotherapy procedure as mentioned or in the form of ice-pop eating has been also observed in patients receiving high-dose melphalan. Besides vasoconstriction, a perhaps temperature-dependent control of melphalan cytotoxicity has been proposed to be responsible for the observed effects [149,150].

The helium–neon laser and other soft lasers have been reported to produce analgesia and wound healing. Studies of laser effects in humans have generally documented decreased pain, inflammation, and oedema in laser-treated tissues. Effects of these lasers on tissues are biochemical (nonthermal); however, the cellular mechanisms of these effects remains elusive [151,152]. A significant reduction of 5-FU or BMT conditioning regimen-induced oral mucositis has been reported in patients, whose oral mucosa was treated by these lasers [153–156].

4. Systemically applied pharmacotherapeutics

Beta carotene, a vitamin A derivative, is a scavanger of singlet oxygen [157]. It also has significant inhibitory effects on cellular proliferation [158]. In an experimental model, beta carotene supplementation decreased local and systemic toxic effects in irradiated mice [159]. Supplemental dietary beta-carotene led to a mild decrease in the severity of chemotherapy- and radiotherapy-induced oral mucositis in a small study [157].

Azelastine hydrochloride is an antioxidant [160] and a potent histamine H1-receptor antagonist [161]. It suppresses neutrophil respiratory burst both in vivo and in vitro and suppresses cytokine release from lymphocytes [160]. Its prophylactic use reduced the severity of chemo-radiotherapy-induced oral mucositis; the result was of little clinical value, however [160].

Pentoxifylline is a xanthine derivative, a haemorrheologic agent, that has been shown to possess profound immunomodulatory properties in vitro, including inhibition of tumor necrosis factor alpha production [162,163]. Elevated levels of tumor necrosis factor alpha have been shown to correlate with both the development and severity of transplantation-related complications [164]. In a phase I–II trial, oral pentoxiphylline reduced the frequency and severity of all major complications after BMT, including reduction of oral mucositis severity [165]. However, these results were not reproduced in other studies including the one focused on 5-FU-induced oral mucositis [166–170].

Indomethacin is a nonsteroidal anti-inflammatory drug inhibiting prostaglandin synthesis. It has been reported to delay the onset of mucositis [171].

Treatment with low-dose intramuscular immunoglobulin has been shown to decrease the severity and duration of radiotherapy-induced oral mucositis [172–174]. Prophylactical application of low-dose intramuscular immunoglobulin reduced chemoradiotherapy-induced oral mucositis in patients with head and neck cancer; this reduction lacks clinical relevance, however [175]. Intermediate dose intravenous immunoglobulin G has been observed to prevent high-dose methotrexate-induced oral mucositis [176]. It is probable that anti-inflammatory effects of exogenous immunoglobulin are responsible for the observed effects. Large infusions of immunoglobulin G have been shown to manipulate the immune system; T cell effector and regulatory functions can be manipulated; inflammatory cytokine release

downregulated and complement activation modified [177,178]. In addition, high TGF-β concentrations have been detected in intravenous immunoglobulin preparations [179].

Anticholinergic drugs cause xerostomia by decreasing salivation, which may result in decreased mucosal secretion of certain cytostatic agents and thus reduce their acute toxicity to oral mucosa. Propantheline reduced significantly oral mucositis in patients treated with high-dose etoposide both as single-agent and in multidrug regimen [180,181]. Atropine has not been shown to be beneficial in the prevention of high-dose methotrexate-induced oral mucositis [132].

The mucosal protection effects of granulocyte colony-stimulating factor G-CSF or GM-CSF were observed in patients treated with various chemotherapy regimens [23,182–185], although controversies exist in other clinical trials [186–188]. These studies focused primarily on the myelocytic recovery effect of CSFs on intensive chemotherapy-induced neutropenia. Results of studies evaluating the effect of these cytokines on oral mucositis have confirmed that they are beneficial in reduction of this complication [16,25,189–192]. There are two theories on the mechanism of oral mucositis reduction by G-CSF and GM-CSF. The first one supposses that neutropenia may predispose the patient to oral infections, which may aggravate oral mucositis. G-CSF or GM-CSF may reduce oral mucositis by accelerating neutrophil recovery. The second, more likely mechanism may be a direct stimulative effect of G-CSF or GM-CSF on the growth or regeneration of oral mucosa cells [16,23,25].

Recombinant human interleukin-11 is a pleiotropic cytokine that stimulates bone marrow stem cells to proliferate and exerts effects on the gastrointestinal mucosa which ameliorate responses to injurious stimuli [193]. It has been reported to favorably modify the course of oral mucositis following 5-FU in hamsters [193–195]. This seems to be mediated at the epithelial or connective tissue level rather than through the bone marrow [194].

Reactivation of oral herpes simplex virus is very common in patients receiving cytotoxic chemotherapy or BMT; its incidence rate ranges between 50 and 90% [15,196–199]. However, herpes simplex virus is probably not the major etiologic agent in chemotherapy- and radiotherapy-induced oral mucositis. The incidence of ulcerative mucositis in BMT patients was observed to be high despite the absence of herpes simplex virus and patients who were seronegative were just as likely to develop mucositis as patients who were seropositive, with comparable healing time of ulcers [15,200–202]. Although *acyclovir* prophylaxis is effective in preventing oropharyngeal shedding of the virus in herpes simplex virus seropositive patients receiving intensive chemotherapy or BMT [197,199,201,202], it did not influence chemotherapy-, radiotherapy-, and BMT-related oral toxicity [201,203–205].

Glutamine is an amino acid synthetized by virtually all tissues and it is an important metabolic substrate for rapidly replicating cells, particularly gastrointestinal tract mucosa and immune cells [206]. During episodes of catabolic stress there is a marked intracellular depletion of glutamine [207]. Parenteral glutamine supplementation appeared to maintain gut integrity in catabolic states in both animal and human studies [208–210] and benefits have also been observed with its enteral administration in methotrexate-related intestinal mucosa toxicity [211]. Oral glutamine supplementation decreased chemotherapy-induced oral mucositis [212,213]; however, no significant positive clinical effect of parenteral or oral glutamine has been observed in two other studies [214,215].

The pineal hormone melatonin inhibits the production of free radicals that mediate the toxicity of chemotherapy. Experimental data have suggested that it may counteract chemotherapy-induced toxicity. Chemotherapy-induced stomatitis was not reduced in a study, although other toxic effects were decreased [216].

5. Other methods

Modification of the chemotherapy regimen may lower it's oral toxicity. In the relapsed childhood acute lymphocytic leukemia study of ALL-REZ BFM (Berlin–Frankfurt–Münster)-85, exposition time to methotrexate was observed to be an important factor of mucosa toxicity. Mucosa toxicity was higher in patients treated by intermediate-dose methotrexate in a 36-h infusion than in patients treated by high-dose methotrexate in a 4-h infusion. The end therapy result was similar in both groups [217]. Similar observation of the influence of exposition time on oral mucosa toxicity was made in patients with nasopharyngeal carcinoma treated by cisplatin, 5-FU, and leucovorin (PFL) combination chemotherapy. Using a weekly 24-h infusion schedule of PFL chemotherapy eliminated severe grades of oral mucositis compared to the 5- or 4-day continuous infusion forth- or third-weekly. The significant anticancer activity was retained in the new weekly regimen [26].

The toxic effects of cancer chemotherapy vary according to dosing time because of the effects of circadian rhythms on cellular or proliferative activity [218]. In human oral mucosa, as in other tissues, DNA synthesis, a stage of cell division cycle associated with increased susceptility to S-phase-specific agents, decreases by 50% or more between 00:00 and 04:00 compared with daytime [218–220]. Severe mucositis occured in about five times more patients and about 10 times more

courses in patients with metastatic colorectal cancer treated by constant rate infusion of oxaliplatin, FU, and folinic acid than in patients treated by a *chronomodulated infusion* (i.e. oxaliplatin administered during the day hours and FU and folinic acid administered during the night and morning hours). The antitumor effect was greater in the chronomodulated group [221].

6. Conclusion

The long list of solutions, drugs and methods used and studied in the prophylaxis and therapy of chemotherapy- or radiotherapy-induced oral mucositis reflects the need of new, more efficient tools in the management of this complication. Many studies involve only small numbers of patients, which militates against the statistical validity of the reported results that must, therefore, be interpreted with caution. Large studies designed to detect substantial clinical differences are often absent. At the present time, no agent has been shown to be uniformly efficacious and can be accepted as standard therapy. Results of national surveys showed great diversity of mucositis management practices, many of which lack proven clinical efficacy [222–224].

Dental restoration and oral hygiene are basic measures. Oral cooling is a cheap and available method to lower the severity of bolus 5-FU- and melphalan-induced oral mucositis; however, more effective methods are needed. The results of the studies with GM-CSF or G-CSF are promising. Lasers have been shown to be partly beneficial; however, a disadvantage of this method is being equipment-demanding. The modification of the chemotherapy regimen resulting in shortening of the exposition time to chemotherapy agents lowers mucosal toxicity of cisplatin, 5-FU, and leucovorin combination chemotherapy, of high-dose methotrexate, and maybe other regimens. Chronomodulation of chemotherapy might also be helpful. The results of animal studies with locally applied TGF-β3 and interleukin-11 are also promising. Based on the findings of the role of the inflammatory cascade involved in normal tissues response to chemotherapy and irradiation, further studies should focus on the use of anti-inflammatory drugs. Thalidomide, a drug with immunemodulating activities, which has been reported to be effective in the treatment of aphthous ulcerations of the mouth and oropharynx in patients with human immunodeficiency virus infection, may also deserve study in the management of anticancer therapy-induced oral mucositis [225].

Systematic prospectively designed investigations are necessary in order to achieve a further reduction in the radiotherapy- and chemotherapy-related acute morbidity [224].

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